CLAIM AMENDMENTS

1. **(Original)** A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of

(i) an α_2-adrenergic receptor antagonist and

(ii) an atypical antipsychotic neuroleptic which has a greater antagonist affinity for D_2 dopamine receptor than its antagonist affinity for α_2 adrenergic receptor in a pharmaceutically acceptable carrier.

2. **(Original)** A method as claimed in claim 1, wherein said α_2-adrenergic receptor antagonist (i) is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

3. **(Original)** A method as claimed in claim 2 wherein said α_2-adrenergic receptor antagonist (i) is idazoxan.

4. **(Original)** A method as claimed in claim 1, wherein said antipsychotic neuroleptic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

5. **(Original)** A method as claimed in claim 1, wherein said α_2-adrenergic receptor antagonist (i) is administered in an amount from about 60 to 120 mg/day.

6. **(Original)** A method as claimed in claim 1, wherein said serious psychotic mental illness is schizophrenia.

7. **(Withdrawn)** A pharmaceutical composition comprising a combination of (i) an α_2-adrenergic receptor antagonist, (ii) an atypical antipsychotic neuroleptic which has a greater antagonist affinity for D_2 dopamine receptor than its antagonist affinity for α_2 adrenergic receptor, and (iii) a pharmaceutically acceptable carrier, wherein the amount

of said ingredients (i) and (ii) is therapeutically effective against serious psychotic mental illness.

8. **(Withdrawn)** A composition as claimed in claim 7, wherein said α_2-adrenergic receptor antagonist (i) is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

9. **(Withdrawn)** A composition as claimed in claim 8, wherein said α_2-adrenergic receptor antagonist (i) is idazoxan.

10. **(Withdrawn)** A composition as claimed in claim 7, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

11. **(Withdrawn)** A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of (i) an α_2-adrenergic receptor antagonist and (ii) an atypical antipsychotic in a pharmaceutically acceptable carrier, wherein said serious psychotic mental illness is selected from the group consisting of Schizophreniform Disorder, Severe Schizoaffective Disorder with Psychotic Features, Bipolar I Disorders with a Single Manic Episode, Severe Bipolar I Disorders with Psychotic Features, Major Depressive Disorders Manifesting a Single Episode, Severe Major Depressive Disorders with Psychotic Features, Bipolar I Disorders Manifesting a Mixed Most Recent Episode, Severe Bipolar I Disorders with Psychotic Features, Brief Psychotic Disorders, Psychotic Disorders NOS, Paranoid Personality Disorders, Schizoid Personality Disorders, Schizotypal Personality Disorders with Sedative, Hypnotic, or Anxiolytic Manifestations, Major Depressive Disorders with Recurrent Episodes, and Psychotic Disorders due to Specific General Medical Conditions.

12. **(Withdrawn)** The method as claimed in claim 11, whereto said α_2-adrenergic receptor antagonist (i) is one or more selected from the group consisting of idazoxan,

yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

13. **(Withdrawn)** The method as claimed in claim 11, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

14. **(Withdrawn)** The method as claimed in claim 11, wherein said α_2-adrenergic receptor antagonist (i) is administered in an amount from about 60 to 120 mg/day.

15. **(Original)** A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of (i) a compound having combined D_2 dop amine and $5HT_2$ serotonin antagonist activities, wherein said compound (ii) has a greater antagonist affinity for D_2 dopamine receptor than its antagonist affinity for α_2 adrenergic receptor and (ii) a compound having α_2 adrenergic receptor antagonist activity.

16. **(Original)** The method of claim 15 wherein said D_2 dopamine and $5HT_2$ serotonin antagonist is an atypical antipsychotic drug.

17. **(Original)** The method of claim 16 wherein said atypical antipsychotic is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

18. **(Original)** The method of claim 15 wherein said α_2-adrenergic receptor antagonist is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

19. **(Original)** The method of claim 18 wherein said α_2-adrenergic receptor antagonist is idazoxan.

20. **(Original)** The method of claim 15 wherein said D_2 dopamine and $5HT_2$ serotonin

antagonist is olanzapine.

21. **(Original)** A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of idazoxan and olanzapine.

22. **(Cancelled)**

23. **(Original)** The method of claim 15 wherein said D_2 dopamine and $5HT_2$ serotonin antagonist comprises an in vivo D_2 occupancy of approximately 50%.

24. **(Withdrawn)** The method of claim 15 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

25. **(Original)** The method of claim 15 wherein said serious psychotic mental illness is schizophrenia.

26. **(Original)** A method for treating a serious psychotic mental illness in a patient in need thereof which comprises co-administration of (i) a compound having combined D_2 dopamine and $5HT_2$ serotonin antagonist activities, wherein said compound has a greater antagonist affinity for D_2 dopamine receptor than its antagonist affinity for α_2 adrenergic receptor, and (ii) a compound having α_2 adrenergic receptor antagonist activity, wherein said compound (i) is administered initially alone in an amount and for a period of time

sufficient to stabilize said patient and subsequently said compound (ii) is co-administered in an amount and for a period of time that allows for a reduction in the amount of compound (i) administered to said patient.

27. **(Original)** The method of claim 26 further comprising the step of reducing the amount of compound (i) administered to said patient after commencing co-administration of compound (ii).

28. **(Cancelled)**

29. **(Withdrawn)** The method of claim 26 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

30. **(Original)** The method of claim 26 wherein said serious psychotic mental illness is schizophrenia.

31. **(Original)** A method for treating a serious psychotic mental illness comprising the step of administered to a patient in need of such treatment a therapeutically effective amount of a combination of (i) a compound that blocks or down-regulates D_2 dopamine and $5HT_2$ serotonin receptor activities and (ii) a compound that blocks or down-regulates α_2 adrenergic receptor activity.

32. **(Withdrawn)** The method of claim 31 wherein said compound (ii) is a

norepinepherine reuptake inhibitor.

33. **(Withdrawn)** The method of claim 31 wherein said compound (ii) is a selective serotonin reuptake inhibitor.

34. **(Withdrawn)** The method of claim 31 wherein said compound (ii) is an anti-sense RNA molecule.

35. **(Original)** A method for treating a serious psychotic disorder in a patient in need thereof which comprises administering an atypical antipsychotic in combination with an effective amount of an α_2 antagonist to provide antipsychotic effects at D_2 receptor occupancy levels of less than or equal to 60%.

36. **(Original)** The method of claim 35 wherein the D_2 occupancy levels are less than or equal to 50%.

37. **(Original)** The method of claim 36 wherein D_2 occupancy levels are measured by positive emission tomography (PET) or single photon emission computerized tomography (SPECT).

38. **(Original)** The method of claim 35 wherein the α_2 antagonist is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan, and atipamezole.

39. **(Original)** The method of claim of 35 wherein the atypical D_2 antagonist is selected from the group consisting of olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

40. **(Original)** The method of claim 35 wherein the atypical antipsychotic and the α_2 antagonist are administered separately.

41. **(Original)** The method of claim 35 wherein the atypical antipsychotic and the α_2

antagonist are administered in combination.

42. **(Original)** The method of claim 41 wherein the atypical antipsychotic and the α_2 antagonist are in different compositions.

43. **(Original)** The method of claim 41 wherein the atypical antipsychotic and the α_2 antagonist are in the same composition.

44. **(Original)** The method of claim 35 wherein one or both of the atypical antipsychotic and the α_2 antagonist comprise a mixture of enantiomers of said compounds.

45. **(Original)** The method of claim 44 wherein the atypical D_2 antagonist mixture comprises from 95/5 to 5/95 mole ratios of the enantiomers of the particular atypical antipsychotic compound.

46. **(Original)** The method of claim 44 wherein the α_2 antagonist mixture comprises from 95/5 to 5/95 mole ratios of the enantiomers of the particular α_2 antagonist compound.

47. **(Original)** The method of claim 35 wherein one or both of the atypical antipsychotic and the α_2 antagonist is administered substantially in the form of a single enantiomer.

48. **(Original)** The method of claim 47 wherein the α_2 antagonist is administered substantially in the form of a single enantiomer

49. **(Original)** The method of claim 48 wherein the (+) enantiomer of idazoxan is administered.

50. **(Withdrawn)** The method of claim 35 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe

bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

51. **(Original)** The method of claim 35 wherein the serious psychotic disorder is child or early adolescent schizophrenia.

52. **(Original)** The method of claim 51 wherein patient in need of treatment is from about age 9 years to 15 years.

53. **(Original)** The method of claim 51 wherein the serious psychotic disorder is childhood onset schizophrenia.

54. **(Withdrawn)** A method for treating a serious psychotic disorder in a patient in need thereof which comprises administering an atypical antipsychotic in combination with an effective amount of a compound which enhances noradrenergic synaptic activity to provide antipsychotic effects at D_2 receptor occupancy levels of less than or equal to 60%.

55. **(Withdrawn)** The method of claim 54 wherein the D_2 occupancy levels are less than or equal to 50%.

56. **(Withdrawn)** The method of claim 54 wherein D_2 occupancy levels are measured by positive emission tomography (PET) or single photon emission computerized tomography (SPECT).

57. **(Withdrawn)** The method of claim 54 wherein the compound which enhances

noradrenergic synaptic activity chosen from the group consisting of reboxetine, atomoxetine, or a compound that inhibits the norepinephrine transporter.

58. **(Withdrawn)** The method of claim of 54 wherein the atypical D_2 antagonist is selected from the group consisting of olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

59. **(Withdrawn)** The method of claim 54 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

60. **(Withdrawn)** The method of claim 54 wherein the serious psychotic disorder is child or early adolescent schizophrenia.

61. **(Withdrawn)** The method of claim 60 wherein patient in need of treatment is from about age 9 years to 15 years.

62. **(Withdrawn)** The method of claim 60 wherein the serious psychotic disorder is childhood onset schizophrenia.

63. **(Original)** A method of treating a serious psychotic disorder involving the administration of at least one atypical antipsychotic and at least one α_2 adrenergic receptor antagonist wherein the improvement comprises selecting atypical antipsychotics and α_2 receptor antagonists such that the receptor affinity ratios for D_2/α_2 ranges from

about 0.8 to about 4.5.

64. **(Original)** The method of claim 63 wherein the ratio of D_2/α_2 ranges from about 0.85 to about 3.9.

65. **(Original)** The method of claim 63 wherein the ratio of D_2/α_2 from about 0.95 to about 1.05.

66. **(Original)** The method of claim 63 wherein the ratio of D_2/α_2 ranges from about 0.95 to 1.00.

67. **(Original)** The method of claim 63 wherein the ratio of D_2/α_2 is about 1.0.

68. **(Withdrawn)** A method for treating a serious psychotic illness comprising administering at least one atypical antipsychotic and at least one α_2 adrenergic receptor antagonist wherein the dosage proportions between the atypical antipsychotic and α_2 antagonist is equivalent to a ratio of 900-1100 mg equivalents of chlorpromazine and an amount of an α_2 antagonist that provides for about equal D_2/α_2 receptor saturation.

69. **(Withdrawn)** The method of claim 68 wherein the amount of D_2 antagonist is equivalent to about 950-1050 mg equivalents of chlorpromazine.

70. **(Withdrawn)** The method of claim 68 wherein the α_2 antagonist is selected from the group consisting of idazox an, yohimbine, ethoxyidazoxan, fluperox an, and atipamezole.

71. **(Withdrawn)** The method of claim 68 wherein the atypical D_2 antagonist is selected from olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

72. **(Withdrawn)** A method for identifying compounds that are useful to treat serious psychotic mental illness which comprises subjecting a candidate compound to an assay demonstrating affinity for the D_2 dopamine receptor and an assay demonstrating affinity

for the α_2 adrenergic receptor and determining that the compound demonstrates significant affinity for both the D_2 dopamine receptor and the α_2 adrenergic receptor.

73. **(Withdrawn)** The method of claim 72, further comprising the step of determining that the candidate compound comprises between about 2 to about 15 fold greater affinity for the α_2 adrenergic receptor than for D_2 receptor.

74. **(Withdrawn)** The method of claim 72 further comprising the step of subjecting the candidate compound to an assay demonstrating affinity to $5HT_2$ serotonin receptors and determining that the compound does not demonstrate significant affinity for the $5HT_2$ serotonin receptors.

75. **(Withdrawn)** A method for treating a serious psychotic mental illness comprising the step of administered to a patient in need of such treatment a therapeutically effective amount of a compound identified by the methods of any of claims 72-74.

76. **(Withdrawn)** A pharmaceutical composition for treating a serious psychotic mental illness comprising a therapeutically effective amount of a compound identified by the methods of any of claims 72-74 and a pharmaceutically acceptable carrier.

77. **(Previously Presented)** A method for treating a serious psychotic mental illness comprising administering to a patient in need of such treatment a combination of idazoxan and
olanzapine in a pharmaceutically acceptable carrier.

78. **(Previously Presented)** The method of claim 77, wherein the idazoxan is administered to the patient at about 1.5 mg/kg.

79. **(Previously Presented)** The method of claim 77, wherein the olanzapine is administered to the patient at about 2.5 mg/kg.

80. **(Previously Presented)** The method of claim 77, wherein the idazoxan is administered to the patient at about 1.5 mg/kg and the olanzapine is administered to the patient at about 2.5 mg/kg.